

Chapter 10

Conclusions, recommendations and implementation strategy

The global plasma fractionation industry, together with individual countries' national arrangements for supplying blood and blood products, plays a major role in contributing to enhanced health care for many millions of people throughout the world. Over 400 000 people in Australia receive a blood product each year, and it is estimated that more than 50% of Australians will require blood or blood products in their lifetime.

Just as there are many people in this country who are recipients of blood and blood products, so there are large numbers of Australians who voluntarily donate blood or plasma on a regular basis. In so doing, these donors make a unique and vital contribution to the health and wellbeing of others – it is difficult to conceive of a more personal or altruistic contribution to one's community than a gift that is, in the most fundamental sense, a gift of the self. Within the wider landscape of voluntary community service, the blood or plasma donor is exceptional. Not only do donors rarely know those who will benefit from their goodwill, but their gift can be a donation of life itself.

The remarkable generosity of the Australian donor community is at the very heart of Australia's national blood arrangements. Also playing a vital role is the Australian Red Cross Blood Service (ARCBS), an operating division of the Australian Red Cross Society. From modest beginnings, the ARCBS has evolved to become a world-class blood service. Currently charged with all collections of Australian blood and plasma, the Australian Red Cross in its capacity as a humanitarian organisation has enjoyed community regard and respect for nearly a century. The association between the Australian Red Cross and Australia's blood supply system is therefore likely to instil confidence in donors, and potential donors, for years to come.

The third major participant in the supply of plasma products to the Australian community is CSL Limited, which, through its CSL Bioplasma business unit, is the national fractionator. Since its foundation in 1916 as the Commonwealth Serum Laboratories, CSL Limited has made a key contribution to health care in this country, not only through the company's fractionation activities but also through its cutting edge research and through the production of vaccines and other pharmaceutical products in quantities sufficient to enable Australia's health system to respond quickly and effectively to emerging public health crises.

The global industry

The global market for plasma derived products, and recombinant alternatives, has a combined value of close to US\$10.5 billion per annum. The market is dynamic, complex and highly competitive, and in respect of some products there is virtually unrestricted global trade.

Review of Australia's Plasma Fractionation Arrangements

There has been dramatic change over the past 20 years in the global plasma products industry, due mainly to mergers and acquisitions, the emergence of recombinant alternative products, and increasing safety requirements. The industry is particularly geared to supplying the needs of markets in Europe, Asia and North America, which between them account for 90% of total world demand for fractionated products.

Annual global plasma fractionation capacity is around 34 million litres. Commercial enterprises account for 81% of this capacity, while the state-owned and not-for-profit share is 19%. The global industry is dominated by six commercial fractionators, of which CSL Limited is the largest. The other five major players are Baxter Healthcare (United States), Talecris Biotherapeutics (United States), Grifols (corporate headquarters in Spain), Octapharma (headquarters in Switzerland), and Kedrion (headquarters in Italy). Talecris, Kedrion and Octapharma are solely concerned with plasma products, while the other companies have more diverse businesses and product ranges. Baxter Healthcare is the largest enterprise overall, with a global turnover of US\$9.8 billion, of which plasma fractionation accounts for 14%. Plasma collection and fractionation account currently for 90% of CSL Limited's global sales revenue.

Consolidation and rationalisation within the industry in recent years have resulted in an increase in the average capacity of fractionation plants (although fewer plants remain). In the United States, average plant capacity is now just over 1.1 million litres, whereas 20 years ago it was around 570 000 litres.

The United States is the only country in the world that is totally self-sufficient in whole blood and in the full range of plasma products. Some 70% of the plasma collected globally is collected in the United States. Domestic consumption absorbs under 40% of this plasma, and over 60% is exported, either as finished product or as starting plasma.

In other countries, national arrangements for the collection of plasma reflect domestic demand together with a diversity of economic, demographic and historical considerations. Canada, for example, in 2005 collected from domestic donors only 24% of the plasma required for the production of domestic IVIg requirements, relying on the United States for the balance. The United Kingdom is wholly dependent on US donors for its supply of plasma, due to the advent of the bovine spongiform encephalopathy (BSE) epidemic in the 1980s: plasma is collected in the United States for UK use and is subsequently transported to Britain for fractionation. Europe is increasingly opening up to greater movement of plasma, and finished plasma products, across national borders. Australia's arrangements for the collection of plasma are discussed in detail below.

The supply of plasma products in the 25 European Union member states and in the United States is frequently via the open market, reflecting, in many instances, health systems in which public sector agencies and funding do not play a key role in the plasma sector.

While many developed countries have plasma fractionation facilities, toll fractionation – whereby plasma collected in one country is processed in another on a fee-for-service basis – is becoming increasingly common. Canada's plasma is fractionated in the United States by Talecris. Plasma from Belgium and Finland is

processed by the Dutch not-for-profit foundation Sanquin, in both Belgium and the Netherlands. Plasma collected in Norway is fractionated by Octapharma, in Austria and in Sweden. CSL Behring toll fractionates for Denmark. Plasma from Poland is fractionated in Austria by Baxter Healthcare. The Laboratoire Français du Fractionnement et des Biotechnologies (LFB), a majority state-owned company in France, fractionates plasma collected in Belgium, Luxembourg, Brazil and Morocco. Brazil's plasma is also processed by other fractionators in Europe. Plasma from New Zealand, Malaysia, Singapore and Hong Kong is fractionated by CSL Bioplasma in Australia.

The reasons a country enters into toll fractionation arrangements with an offshore fractionator usually relate either to a level of demand for plasma products that is insufficient to support a domestic fractionator, or to the considerable financial and technological resources, and technical expertise, required for the operation of a domestic fractionation industry. Those European countries that have elected to toll fractionate generally collect less than 100 000 litres of plasma per annum.

Individual fractionators seek to maximise both yield and product range, although within the parameters imposed by market demand. No single fractionator, therefore, produces the complete range of plasma derivatives, which encompasses albumin, immunoglobulins (including hyperimmune immunoglobulins), and coagulation factors. Hyperimmune production is particularly specialised. It is low-volume, high-value and of limited commercial interest to most fractionators.

Global market for plasma products

The global market for plasma products grew by 5% between 2003 and 2005 and is forecast to expand by a further 11.5% between 2005 and 2008. Products expected to experience significant growth in the immediate future are intravenous immunoglobulin (IVIg), alpha-1 antitrypsin, fibrin sealants, and minor coagulant products. Albumin sales and sales of plasma derived Factor VIII and Factor IX are forecast to grow only modestly.

Global demand for IVIg, commercially by far the most important of the plasma derivatives and currently accounting for some 40% of total demand, is projected to grow from around 78 tonnes in 2006 to 129 tonnes in 2016. The use of IVIg for new indications, changes in clinical practice, or entry by the product into additional markets, could generate demand beyond these levels.

Demand for IVIg worldwide reflects strong and expanding markets in the United States and Europe and steady demand in other developed countries and regions. There is less demand for IVIg and other high-cost plasma products in developing countries, and it is likely to be a considerable time before China (where the major driver of demand is albumin), India, the Middle East and Africa exert significant influence upon the world market. Rising income levels and improved health standards worldwide will ultimately, however, have an impact upon global demand.

Until the mid 1990s, plasma derived Factor VIII was the driving product for plasma fractionators. By 2002, however, demand for recombinant alternatives, which had first become available in 1994, had overtaken demand for the plasma derived product. For

Review of Australia's Plasma Fractionation Arrangements

various reasons – among them, clinical preferences and the emergence of immune tolerance and inhibitor issues for some people treated with the recombinant form – demand for plasma derived Factor VIII has nevertheless continued to grow, albeit at a much slower rate than that exhibited by the recombinant form. Annual global demand for plasma derived Factor VIII is forecast to increase from 2240 million international units (IU) in 2006 to 2612 million IU in 2016. Demand for recombinant Factor VIII is projected to grow from 2767 million IU to 4735 million IU over the same period.

Worldwide demand for albumin is forecast to grow from 474 tonnes in 2006 to some 544 tonnes in 2016.

In any discussion of current and future demand for plasma derived products, it is important to record that at present an estimated 15% of the world's population consume over 90% of the world's plasma product output. It is of considerable concern to the world community, and in particular to the World Federation of Hemophilia and its member organisations, that in developing countries very few people with haemophilia have access to the products they need in order to increase life expectancy.

Australia's arrangements

Australia's arrangements with respect to the supply of fresh blood and fractionated plasma products are unique and are not replicated in any other country. The close engagement of key government agencies with the role of the not-for-profit Australian Red Cross Blood Service as collector of blood and plasma, and with the role of CSL Bioplasma as the national fractionator – and the generosity of Australia's many voluntary, non-remunerated blood and plasma donors – are factors that combine to create a world-class blood system.

Governance

The National Blood Agreement (2003) between the Commonwealth and the states and territories provides the framework within which blood and blood products are funded and are supplied to the Australian community. Under the Agreement, the Australian Health Ministers' Conference (AHMC), a committee comprising the health ministers of Australia's nine jurisdictions, has responsibility for the oversight and management of the Australian blood sector. The National Blood Authority (NBA), a federal agency, manages the national blood supply system on behalf of Australia's governments, monitoring demand for blood and blood products, managing procurement arrangements with product suppliers, and undertaking annual supply planning and budgeting.

The NBA is overseen by the Jurisdictional Blood Committee (JBC), which operates on behalf of Australia's health ministers and is a subcommittee of the Australian Health Ministers' Advisory Council (AHMAC). Representing the perspectives of the individual jurisdictions, the JBC considers national policy, ongoing demand for blood and blood products, supply planning, product distribution, funding, and emerging products, services and technologies, and provides advice and support to AHMC on these matters.

The Review notes that in its short period of existence the NBA has been conspicuously successful in ensuring greater value for governments, particularly in relation to pricing negotiations for albumin and recombinant Factor VIII.

Policy

Under the National Blood Agreement, policy setting is a joint function of the Commonwealth, state and territory governments, and includes responsibility for compiling the annual National Supply Plan, for developing best-practice systems and for considering policy issues associated with the supply and administration of blood and blood products in clinical settings.

The Jurisdictional Blood Committee has a key support role in seeking evidence-based advice on the safety, quality, efficacy and cost-effectiveness of existing or proposed blood-related products, services or other activities; and in arranging for the preparation of evidence-based guidelines promoting the safe, efficient and effective collection, distribution, storage and use of blood and blood products in Australia.

Regulatory framework

The Therapeutic Goods Administration (TGA), an arm of the Australian Government Department of Health and Ageing, carries out a range of assessment and monitoring activities to ensure that therapeutic goods available in Australia are of an acceptable standard, and that the Australian community has access, within a reasonable time, to therapeutic advances. In order to obtain TGA approval for release in Australia, both imported and domestic therapeutic products must meet the same safety standards and regulatory requirements.

Plasma products are subject to the highest standard of regulation applicable to therapeutic goods. Because they are sourced from humans, these products, classified as biologicals, carry an inherent risk of transmitting acquired pathogens. Product safety is therefore of paramount importance and is guarded by stringent TGA regulations throughout the supply and manufacturing chain. At the point of donation, the Australian Red Cross Blood Service operates strict donor screening and deferral policies, and tests individual donations for key viral markers. Prior to its pooling for fractionation, the plasma is subjected to further rigorous testing at the CSL Bioplasma plant, while purification and viral-inactivation measures are undertaken by CSL during the manufacturing process. These mandatory viral-inactivation procedures are critical to ensuring the safety of plasma products.

The TGA conducts regular audits, announced and unannounced, of the CSL Bioplasma plant.

Funding

Responsibility for funding Australia's national blood arrangements is shared by the Commonwealth, state and territory governments. The Commonwealth provides 63% of the funding, and the remaining 37% is sourced from the states and territories. A National Supply Plan and Budget for blood and blood-related products and services is approved by the Australian Health Ministers' Conference on an annual basis. The Supply Plan is based upon the recommendations of the Jurisdictional Blood

Review of Australia's Plasma Fractionation Arrangements

Committee and requires each jurisdiction's authorisation before implementation of changes with financial implications.

In 2005–06 the cost to Australian governments of providing patients with fresh blood products, plasma products and recombinant alternatives was \$565.4 million. This figure incorporates \$297.7 million to the Australian Red Cross Blood Service to provide fresh blood products, to collect plasma for fractionation, and to manage distribution and support services; \$136.8 million to CSL Limited for plasma product production and for imported products; and \$130 million to other suppliers (Baxter Healthcare \$68.5 million; Novo Nordisk \$23.6 million; Octapharma \$22 million; and Wyeth \$15.9 million). Expenditure on management of the National Blood Authority in 2005–06 was \$8.2 million. For 2006–07 the total cost of funding Australia's national blood arrangements is estimated to be \$650.7 million. The figures do not include costs (other than the purchase of blood products) associated with treatment in a hospital or with same-day clinical care.

Supply

The great majority of plasma products supplied to the Australian community are manufactured in Australia from domestically sourced plasma. The importance of ensuring an adequate and secure supply of plasma derivatives for Australian patients necessitates the importation of some products, either where clinical demand exceeds what can be provided from domestic plasma collections, or where a required product is low-volume and is not manufactured by CSL Bioplasma. All suppliers of plasma products for use in Australia operate under agreements that ensure both security of supply and reserve stocks of product.

National capacity

Production of plasma derived products in Australia takes place at the CSL Bioplasma plant at Broadmeadows, Melbourne. The plant currently has the capacity to fractionate 500 000 litres of plasma per annum. CSL advises that additions to the existing plant could see capacity increased to 750 000 litres per annum (with existing infrastructure in place) or to 1 million litres per annum (given additional buildings and services on the Broadmeadows site).

Public attitudes

The current system governing the blood sector in Australia, characterised by strong levels of cooperation between federal, state and territory governments, the Australian Red Cross Blood Service, the National Blood Authority and CSL Limited, gives outstanding service to Australians.

CSL's Broadmeadows and Parkville plants are widely perceived as iconic establishments within the biotechnology sector, in terms both of technology and research and development capacity, and employment opportunities provided. CSL Bioplasma Broadmeadows is the only plant of its kind in Australia with the technology and expertise to fractionate efficiently the quantities of plasma collected by the ARCBS from Australian donors.

Across the broad range of local submissions received by the Review Committee, almost universal concern was expressed with regard to any perceived threat, or

likelihood of change, to Australia's current blood arrangements. Maintaining the existing integrity and reliability of these arrangements, and the level of safety at which they function, is seen by stakeholders to be of vital importance.

While the submissions in general did not favour changes to the status quo, particular concern was expressed about the possibility that Australian plasma might be processed overseas. Questions were raised as to whether products manufactured from Australian plasma by offshore fractionators could meet the levels of safety, quality and efficacy currently required of domestically fractionated products, and whether the circumstances of overseas fractionation arrangements would permit the Therapeutic Goods Administration to exercise its appropriate supervisory and regulatory powers.

One issue of stated concern in various submissions was that Australian plasma fractionated overseas might be mixed with plasma from other countries, including those at a greater risk with respect to agents like variant Creutzfeldt-Jakob disease (vCJD), or viral contamination.

Australia's future demand

IVIg

Demand for IVIg is a critical factor in any assessment of demand for plasma products more broadly, as the IVIg requirements of a given jurisdiction set the level of starting plasma it requires for the production of all plasma derived products, excluding hyperimmunes. Over the past decade, demand for IVIg in Australia has increased by 14% per annum. Australian consumption in 2005–06 was 83 grams per 1000 population, which represents a total consumption of 1667 kilograms.

Forecasts provided to the Review suggest that by 2015–16 Australian demand for IVIg will be between 2985 and 3687 kilograms per annum. The average of these two figures, 3336 kilograms, represents more than double the amount of IVIg currently being issued in Australia, and consequently would require more than double the amount of plasma (at current yields). If the Allen Consulting Group forecast of 7.7% annual growth in demand for IVIg proves accurate, Australia will need 686 tonnes of plasma in 2015–16, compared with 308 tonnes in 2005–06: an increase of 123% over the next ten years.

This scenario assumes, based on advice to the Review, that no synthetic substitutes for IVIg are likely to emerge over the next ten years – immunoglobulins are very complicated molecules, and their synthesis via genetic engineering or recombinant technology will prove extremely difficult. The demand for plasma derived immunoglobulins will almost certainly not be met in the near future by the advent of recombinant alternatives.

Albumin

Both the Australian Red Cross Blood Service and the National Blood Authority forecast significant increases in demand for albumin over the coming decade: from 4836 kilograms in 2005–06, to 9355 kilograms and 8150 kilograms respectively by 2015–16. In making these projections, the ARCBS and the NBA point to the increased usage of albumin in the surgical treatment of cardiovascular disease.

Clotting factors

The treatment of haemophilia A and B with Factor VIII and Factor IX respectively was traditionally one of the key reasons for the collection and fractionation of plasma. While these clotting factors brought considerable health benefits to people with haemophilia, for a short period in the 1980s the use of these products resulted in the transmission of viral diseases, such as hepatitis C and HIV, to recipients; although the industry was quick to respond with appropriate viral-inactivation and removal procedures, many people with haemophilia became infected. As a consequence, haemophilia societies around the world campaigned to replace plasma derived Factor VIII and IX with recombinant alternatives.

The decision made by Australia in August 2004 to provide funds to enable all people with haemophilia A and B to have access to recombinant Factor VIII and Factor IX has, to a large extent, ensured a balance between supply and demand for these products. By the end of 2006, around 85% of people with haemophilia A were receiving recombinant Factor VIII.

There will continue to be demand for plasma derived Factor VIII, however, for the treatment of von Willebrand's disease and in circumstances where people prefer or need to continue using plasma derived products.

The National Blood Authority predicts an 11.6% average annual growth rate in the issuing of Factor VIII (both plasma derived and recombinant) in Australia over the next decade, with 12.0 IU per head of population being issued by 2015–16; CSL Limited on the other hand predicts a stable level of demand over the same period. The average of the various forecasts received by the Review suggests that at year 2015–16 there will be an annual demand of 24.75 million IU for plasma derived Factor VIII (assuming that this product will continue to be used by a small number of patients who fare better on the plasma derived form than on its recombinant alternative).

The supply of CSL's plasma derived Factor VIII product Biostat® is complicated by the fact that the Therapeutic Goods Administration requires, as an additional precautionary measure, that the plasma used in the manufacture of this product be collected from donors who have not travelled outside Australia or New Zealand since 1980. In 2005–06, this requirement reduced the starting pool of plasma available for production of plasma derived Factor VIII to approximately 100 tonnes (out of the year's total collections of 308 tonnes), a quantity just sufficient to meet a demand of 15.6 million IU of plasma derived Factor VIII for the year.

If the more ambitious of the forecasts provided to the Review prove to be accurate, it follows that Australia may be obliged to import some plasma derived Factor VIII, sourced from overseas plasma, in future years.

Forecasts with respect to future demand for Factor IX share many of the characteristics of projections for Factor VIII. From a supply point of view, future demand for plasma derived Factor IX can be readily met by normal plasma collections in the foreseeable future.

Future supply of plasma in Australia

A key issue, perhaps *the* key issue, in respect of Australia's current plasma fractionation arrangements is the importance of increasing the volume of plasma collected in this country, in order to meet increasing demand for plasma derived products, especially IVIg.

Over the last ten years, demand for IVIg – which continues to be the driving factor in the plasma products sector – has increased at a rate much higher than the growth in the supply of starting plasma available for fractionation. Since 2003–04, in order to meet demand, the domestic IVIg supply has been supplemented with imported IVIg products.

This situation is not peculiar to Australia but is a global trend; worldwide, there is potential for an ever-increasing unmet demand for plasma products, particularly IVIg.

While CSL Bioplasma strives on an ongoing basis to improve IVIg yields (yields are already high, helping to minimise the supply–demand gap) the central issue is that of blood donations. The Australian Red Cross Blood Service continues to develop strategies for increasing both donor numbers and frequency of donations by existing donors. Australian blood and plasma collection rates are already high by international standards, at 15.3 litres per thousand population. Australian donation trends to date, however, do not offer any certainty that the donor pool can be increased to levels sufficient to provide the quantity of plasma needed to meet forecast demand.

The ARCBS is developing some proposals for strategies that it believes will bridge the supply–demand gap. These include aiming to increase plasma supply via an increase in plasmapheresis collections.

Nevertheless, there is a need both for donor numbers to be augmented very significantly, and for an increase in the proportion of donors prepared to be subjected to the time-consuming and relatively invasive procedure of plasmapheresis (which yields substantially more plasma than whole blood donation). It is also important, though, that the supply of red cell units is maintained through whole blood donations, as there have been shortages of this product in the last year. A related issue is that all strategies for increasing donor numbers and participation rates place considerable additional demand on the resources of the ARCBS.

Self-sufficiency

The promotion of national self-sufficiency in respect of blood and blood products is a policy aim of Australia's Commonwealth, state and territory governments. The Australian Health Ministers' Conference Policy Statement on National Self-Sufficiency in the Supply of Blood and Blood Products, issued in April 2006, defines self-sufficiency as:

Australia striving to source blood components and plasma from within Australia to meet appropriate clinical demand.

The AHMC policy statement continues:

This statement has been developed in response to a number of questions about

Review of Australia's Plasma Fractionation Arrangements

whether recent government decisions to import certain blood products are consistent with the national policy aim relating to promoting national self-sufficiency in the blood supply.

All Australian, State and Territory Governments are signatories to the National Blood Agreement 2003, which sets out, among other things, the policy objectives and aims for Australia's national blood sector.

The primary policy objectives in the National Blood Agreement are to:

- provide an adequate, safe, secure and affordable supply of blood products, blood related products and blood related services; and
- promote safe, high quality management and use of blood products, blood related products and blood related services in Australia.

Underpinning these primary policy objectives are a number of secondary policy aims, including promoting national self-sufficiency. This policy aim has not changed. However, importation of blood products does occur in a narrow range of circumstances where there is an inability to meet clinical needs through the domestic supply, and where supply chain risks must be addressed. This happens within a framework that:

- ensures adequacy of supply to Australian patients in need;
- minimises the supply security and product safety risks to patients;
- ensures affordability of products to the Australian health sector; and
- recognises the practicalities of production and distribution.

The AHMC statement acknowledges that Australia is not totally self-sufficient in plasma products. In fact, Australia has never been self-sufficient in all plasma derivatives. The Review agrees, however, that Australia should be as self-sufficient as possible, and that self-sufficiency should remain an important goal.

Voluntary donors

The principle of voluntary, non-remunerated blood donation was first discussed by the World Health Assembly (WHA) in 1975 and articulated in WHA resolution 28.72. As a member of the WHA, Australia supported this resolution, which urged WHA member states to promote the development of national blood services based on voluntary, non-remunerated blood donation.¹ The main motivation for the resolution was to reduce risk to the blood supply in developing countries and to inhibit exploitation of donors. The most recent reference by the WHA to voluntary, non-remunerated donation occurred in May 2005, in a resolution that exhorts member states to:

establish or strengthen systems for the recruitment and retention of voluntary, non-remunerated blood donors and the implementation of stringent criteria for donor selection.²

1 World Health Organization, *Twenty-Eighth World Health Assembly, Geneva, 13–30 May 1975: WHA28.72 Utilization and Supply of Human Blood and Blood Products*, World Health Organization, Geneva, 1975, <<http://www.who.int/bloodsafety/en/WHA28.72.pdf>>.

2 World Health Organization, *Fifty-Eighth World Health Assembly: WHA58.13 Blood Safety: Proposal to Establish World Blood Donor Day*, World Health Organization, Geneva, 2005, p. 1, <http://www.who.int/bloodsafety/WHA58_13-en.pdf>.

Australia and European countries adhere to the definition of voluntary non-remunerated donation prescribed by the Council of Europe in its publication *Guide to the Preparation, Use and Quality Assurance of Blood Components* (January 2005). The Council of Europe has determined that small tokens, refreshments and the reimbursement of direct travel expenses are compatible with the voluntary and unpaid donation of blood. The Council of the European Union has included a similar provision in its definition of voluntary, non-remunerated donations.³

The question of reimbursement of donors for expenses incurred as a direct consequence of donating blood or plasma has been raised by many stakeholders in the course of the Review. While acknowledging the National Blood Agreement policy aim of maintaining reliance on voluntary, non-remunerated donations of whole blood and plasma, the Review has given consideration to this issue.

Reimbursing donors for travel expenses, or providing a taxation offset to cover part of these expenses, would be a departure from current government policy with regard to volunteerism – which is underpinned by the principle that services performed by volunteers should not attract recompense for costs incurred. It is the opinion of the Review, however, that this approach may need to be reconsidered in the light of the exceptional need to increase the number of blood donors in Australia. The Review would not recommend that Australia consider any system of direct payment to donors. The case for retaining the current system, whereby donors donate freely and without expectation of remuneration, rests not only on issues of WHA advocacy or on precedents in other countries, but – much more importantly – on a sense in the Australian community of the value and merit of the existing arrangements.

Distribution of plasma and plasma products within Australia

The Australian Red Cross Blood Service distributes fresh blood products, and some plasma, directly to hospitals and clinicians. The bulk of the plasma collected by the ARCBS is delivered to CSL Bioplasma for fractionation. Finished plasma products are generally transported from CSL Bioplasma to the ARCBS, which then carries responsibility for their distribution; distribution is effected through ARCBS business units, in cooperation with hospital blood banks, pathology laboratories and clinicians. The ARCBS also undertakes the role of distributor for specific imported plasma products.

There are two exceptions with regard to the distribution of domestically fractionated product: normal immunoglobulin is distributed in some states directly from local CSL facilities, with or without the ARCBS playing a role in ordering; and the 4000 IU IV tetanus product is shipped direct from CSL to customers.

Requests for plasma products for patients can be received by the ARCBS at any time, day or night, making a robust distribution system essential.

Under current National Blood Authority agreements for the supply of certain imported plasma products and recombinant products, distribution of these products is in most cases carried out directly by suppliers.

³ Council of the European Union, 'Council Recommendation of 29 June 1998 on the Suitability of Blood and Plasma Donors and the Screening of Donated Blood in the European Community (98/463/EC)', Official Journal of the European Communities, L 203, vol. 41 (21 July 1998), p. 18; also available online at <http://eur-lex.europa.eu/LexUriServ/site/en/oj/1998/l_203/l_20319980721en00140026.pdf>.

Future fractionation arrangements

The Review has examined very carefully fractionation arrangements in the United States and Europe, and has given close consideration to possible alternative arrangements for Australia.

Any change to the current arrangements, whereby Australia's plasma would be fractionated overseas rather than at a locally based fractionation plant, would require significant initial expenditure, extensive transitional planning, contingency plans, risk mitigation plans, and investment associated with registration and other compliance and approval processes.

The lead times involved in overseas fractionation of Australian plasma would be almost double the current lead times 'vein to vein' (i.e. from donation, through processing and distribution, to the recipient of a finished plasma product).

There would be significant additional costs involved in the overseas manufacture of plasma products for Australia. Some of these costs (e.g. for the transportation of Australian plasma to an overseas fractionation facility, for the return of finished plasma products to Australia, for cold storage and warehouse facilities, etc.) would be borne by the fractionator and reflected in price structures for fractionation services.

Major costs arising from the offshore fractionation of all Australian plasma would include a one-off 'transition cost' of approximately A\$75 million. This amount would be needed for the collection (if feasible) of sufficient additional domestic plasma to cover the 60-day withholding period if required (and the period required for sea transport) and scheduled processing time, or for the one-off purchase of the same quantity of imported finished product. Either strategy would increase the National Reserve from its present target inventory of three months' supply of plasma products, by an additional six months' stockholding.

Any ongoing shortfall in IVIg supply related to the yield of overseas fractionators would need to be addressed via the importation of IVIg products, which would have implications for Australia's national self-sufficiency policy.

Further, there are potential significant risks involved in the overseas fractionation of Australian plasma. While some of these scenarios are of low probability, their consequences would be expensive and disruptive. For example, loss of a 20-foot reefer container of plasma would represent a major disruption to Australian supply and would necessitate the acquisition of overseas-sourced plasma, or of the equivalent in finished products manufactured from overseas-sourced plasma, to compensate.

Conclusions

1. The three key public policy challenges in respect of Australia's future plasma fractionation arrangements are to ensure that:
 - future arrangements maintain the safety, quality and efficacy of plasma products fractionated for Australian use
 - arrangements provide the basis for delivering security of supply of plasma products for Australia
 - future arrangements provide the best possible value for money for Australia.
2. The key drivers of plasma fractionation arrangements for Australia, given projected demand over the next ten years, are intravenous immunoglobulin (IVIg) and plasma derived Factor VIII and Factor IX, and the safe and secure supply of these products must be ensured.
3. If Australia is to be self-sufficient in the plasma required for the production of IVIg, then, given projected demand over the next ten years, a significant increase in domestic plasma collections by the Australian Red Cross Blood Service will be necessary. Achieving this increase will require of all Australian governments vigorous review and reform of current domestic plasma collection arrangements.
4. In any event, Australia will need to maintain imports of plasma derived product in order to meet domestic demand. If the increases in plasma collections projected by the ARCBS are not met, then the requirements for imported products will increase considerably.
5. A key factor in determining the most appropriate plasma fractionation arrangements for Australia are the relative yield rates of potential fractionators. Any change in current arrangements that delivered a lower yield rate would have flow-on implications for costs and logistics, in terms of higher plasma collection requirements or alternative replacement strategies, and additional transport and manufacturing costs. While it is not possible to predict with any accuracy future national or global yield rates, Australia's current fractionation arrangements appear to deliver a very high IVIg yield rate by world standards (more than 5.0 g/L in 2005–06).⁴ It appears unlikely that any other fractionator could presently match the IVIg yield being achieved by CSL Bioplasma.
6. Overseas fractionation of Australian plasma would involve significant transitional costs and, because of yield considerations, there would be the potential for an ongoing shortfall in the supply of IVIg and other plasma derived products. The consequent need to source these products via imports would have implications for the national self-sufficiency policy.
7. There are potential supply chain risks involved in overseas fractionation of Australian plasma. While some of the risk scenarios are of low probability, their consequences would be expensive and disruptive. Addressing these risks would require either an impost on the National Reserve of plasma products or an added call on existing standing offers for imported product.
8. The overseas fractionation of Australian plasma could mean that some products that are not manufactured under the current arrangements could be fractionated using Australian plasma. However, given that the products concerned are of

4 <<http://www.csl.com.au/Investors.asp>>.

Review of Australia's Plasma Fractionation Arrangements

relatively low volume, in comparison to IVIg, albumin and the major clotting factors, their manufacture under these conditions would be of limited benefit to Australia, and unlikely to be economically viable for a fractionator.

9. Any supply to Australia of plasma products from overseas fractionators would require significant lead times and investment in registration and other approval processes. If registration of products were to be a prerequisite to tendering for the supply of plasma products to Australia, not all overseas fractionators would be likely to want to incur the costs of registration in the absence of a supply contract. If, on the other hand, product registration were to be required only after a tender contract had been agreed, then a lead time of at least two years would be needed for registration and approval processes.
10. Increased transparency with respect to collaboration between stakeholders; longer-term planning; and streamlining ordering systems in line with emerging technologies would significantly increase the efficiency of the current distribution system.
11. Public opinion in Australia is strongly in favour of maintaining the current plasma fractionation arrangements, particularly with regard to the role of the ARCBS and the domestic handling of the donation of 'the gift of blood'.
12. When the transitional costs, the risks, and the indeterminate yield ratios of overseas fractionation are considered against the national self-sufficiency objective, and when account is taken of the national strategic importance of CSL's plant at Broadmeadows, then overseas fractionation of Australian plasma is not an advantageous option for Australia.

Recommendations

1. Ministers should note the Review's conclusion that overseas fractionation of Australian plasma is not an advantageous option for Australia. Ministers should also note the substantial regulatory and other changes, as set out in this report, that would be necessary in the event it were desired to alter present arrangements and invite overseas manufacturers to tender for the fractionation of Australian plasma.
2. In view of the prospect of substantial shortfalls between projected demand for plasma products in Australia, and domestic plasma collected by the Australian Red Cross Blood Service, urgent action must be taken to increase plasma collection rates. There needs to be a vigorous and creative campaign, led by Commonwealth, state and territory governments, to energise the community in favour of blood donation.
3. The Commonwealth, state and territory governments should safeguard the security of supply of plasma products for Australians by importing plasma products to address any shortfall and risks in supply of domestically manufactured products. Procurement of imported plasma products should be undertaken by an international competitive tender process, which could include provision for tiered pricing related to the volume of specific products required. This may also facilitate benchmarking by the National Blood Authority of domestically manufactured plasma products against prices for imported plasma products, in order to further

Review of Australia's Plasma Fractionation Arrangements

the objective of value for money in future contract negotiations, consistent with other policies. Existing contracting, risk management and mitigation strategies for Australia's plasma fractionation arrangements should be reviewed by the Australian Health Ministers' Conference in consultation with relevant parties and, where appropriate, upgraded in line with world's best practice.

4. The ARCBS needs to enhance innovation in its marketing efforts and customer service strategies in order to recruit donors from a broader cross section of the Australian community and to retain existing donors. In particular, there is a need for new strategies for encouraging more young Australians and members of ethnic communities to donate blood. The ARCBS will need additional funding support from governments to develop and implement such strategies. In the future, consideration may need to be given as to whether travel costs incurred by blood donors and plasma donors should be reimbursed or permitted to be treated as an allowable taxation offset; taxation offset for costs incurred as a direct consequence of blood or plasma donation would be a powerful statement of the importance attached by Government to the voluntary donation of blood.
5. The present annual planning and budgeting framework for plasma supply should be reviewed, with a view to moving to a four- to five-year business planning cycle. The current annual planning cycle is not consistent with best practice in strategic planning and can limit capacity for ensuring operational efficiency.
6. Uniform provisions concerning the age at which a person is eligible to donate blood should be introduced by all state and territory governments. A uniform approach along the lines of the system operating in South Australia would be in the best interests of collections by the ARCBS.
7. There should be greater consistency between states and territories in the application of revised national guidelines for IVIg usage.
8. The Therapeutic Goods Administration regulatory base should be revised to provide explicitly for the conduct of unannounced audits of overseas manufacturers. The new arrangements should be supported and confirmed through either Mutual Recognition Agreements or provisions in contracts with manufacturers. Consideration should be given to negotiating amendment of the Australia–EC/EFTA MRAs, to enable joint inspections of manufacturers of high-risk medicines (including plasma products) by the TGA and designated EC/EFTA GMP inspectorates, where appropriate. Consideration should be given to amending the Therapeutic Goods Regulations to ensure that fees may be imposed on Australian product sponsors to cover the costs of GMP auditing of overseas manufacturing sites.
9. The Australian Health Ministers' Conference should continue to monitor and assess industry developments, with the aim of ensuring that the range of Australian plasma derived products remains appropriate to clinical requirements.
10. Australia should maintain its reservation regarding the procurement of blood fractionation services under the Australia–United States Free Trade Agreement. The reservation exempts the procurement of plasma fractionation services from the government procurement provisions in Chapter 15 of the Agreement. The CSL Act should also be maintained.

Implementation strategy

1. Contingency

Australia will need to maintain imports of plasma derived products in order to meet future domestic demand. The supply–demand gap will potentially always exist. The current fractionation arrangements agreed by the Australian Health Ministers' Conference provide for the fractionation onshore, by CSL Bioplasma, of all Australian plasma, and for the importation of plasma derived products that either are not manufactured by CSL Bioplasma or, in the case of IVIg, are required in order to augment domestic supply, as a contingency measure. There is therefore the opportunity for international fractionators that wish to compete for this contingency supply business to participate in the Australian market. It is in the national interest that:

- i) The Jurisdictional Blood Committee and AHMC continue to monitor and assess industry developments, both domestic and international, with a view to ensuring that the Australian community continues to benefit from the provision of an appropriate range of safe, efficacious and high-quality therapeutic products derived from human plasma, and that these products are derived from Australian plasma wherever possible, and complemented with imported product only as a contingency measure.
- ii) Risk management and mitigation strategies for Australia's plasma fractionation arrangements be continuously maintained, reviewed and upgraded by the National Blood Authority, as advised by the JBC, in accordance with world's best practice and so as to ensure Australia's ongoing access to safe, high-quality plasma derived products.
- iii) The existing contingency supply arrangements, which involve the negotiation of standing offers, do allow for some limited competitive elements to be introduced into the Australian market, and this arrangement should be used to maximise the opportunity for competition. The procurement of imported plasma products should be undertaken by international competitive tender and could include provision for tiered pricing related to the volume of specific products or type of specific services required.
- iv) The NBA should undertake price benchmarking of domestically manufactured plasma products against prices for imported plasma products to inform future contract negotiations.

2. Collection

All Australian governments should consider the reform of current and future domestic plasma collection arrangements. Following the 2006–07 business study of the efficiency and effectiveness of the Australian Red Cross Blood Service, a comprehensive change agenda may need to be developed.

3. Distribution

The National Blood Authority and the Jurisdictional Blood Committee should initiate a review of current distribution arrangements between the Australian Red

Cross Blood Service and CSL Bioplasma, and should, in particular:

- i) review and reduce the number of stocking points and the number of products stocked at each, having regard for the need to maintain sufficient stocks in strategic locations so as to be able to meet urgent requirements
- ii) set inventory target levels, according to product and demand profiles, and review these target levels on a regular basis and in a systematic manner
- iii) share patient de-identified clinical requirements data (orders data) with all supply chain partners
- iv) facilitate collaboration between supply chain partners, through information transparency
- v) foster collaboration with hospital administrators so as to improve operating efficiencies (e.g. by pre-labelling deliveries with patient identifiers, when and if appropriate)
- vi) develop a range of whole-of-supply-chain performance indicators.

In the longer term:

- i) prepare a formal analysis of the supply chain requirements of different groups of approved health providers
- ii) adopt multiple distribution channels, to the extent that this proves to be the most cost-effective and efficient means of meeting the needs of different end users
- iii) consider combining the strengths of the ARCBS and CSL by developing an improved distribution channel in which the ARCBS services the medical information needs of approved health providers and ensures appropriate clinical use of plasma products, while CSL provides efficient and robust cold chain distribution services. Consideration should also be given to the use of a dedicated specialist cold chain provider to deliver plasma derived and recombinant products provided under the National Blood Agreement.
- iv) encourage approved health providers to develop long-term plans for investment in supply chain enhancements, including greater reliance on e-commerce solutions that work best within the health providers' own environments and that integrate effectively with the systems of other supply chain partners.

4. NBA plasma collection and fractionation agreements

Because of the critical national reliance on National Blood Authority agreements for plasma collection and fractionation, the NBA, in conjunction with all governments and other stakeholders in the health sector, should seek at all times to ensure that such agreements deliver best-practice outcomes on:

- product range, quality and price
- supplier services and performance
- risk mitigation.

Summary assessment

In the light of a comprehensive analysis of the existing system, and following a considered, objective and thorough examination of alternatives, it is concluded that the current structural arrangements whereby domestically collected plasma is fractionated by CSL Bioplasma are, subject to careful monitoring of prices, in Australia's best interests. The present system is well entrenched in the 'hearts and minds' of the Australian population and of the Australian medical community and, particularly, in the strategy, thinking and reliance of all end user groups.